Developmental origin of age-related coronary artery disease.

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Public Summary:
Coronary artery disease, leading to blocked blood flow to the heart, is a major cause of heart attack. Age and injury cause structural and functional changes in coronary artery smooth muscle cells (caSMCs) that influence the progression and severity of coronary artery disease. Although paracrine signalling is widely believed to drive phenotypic changes in caSMCs, here we show that developmental origin within the fetal epicardium can have a profound effect as well. We discovered that caSMCs come from two different sources of epicardial cells during development. We probed the differences between the two different sources of CaSMCs using a transgenetic mutation that ablated the first wave of early migrating cells. Ablation of the early population resulted in coronary arteries consisting solely of late population caSMCs. The resuting coronary arteries appeared normal into early adulthood and the animals showed no signs of disease. However, by middle age (5-8 months of age in the mouse), they became progressively fibrotic, lost the adventitial outer elastin layer, were dysfunctional and leaky, and caused early death. We conclude that heterogeneity in the fetal epicardium that is linked to coronary artery integrity, and that distortion of the coronaries epicardial origin predisposes to adult onset disease. A possible developmental basis for susceptibility to coronary artery disease has been proposed, but never verified until now.

Scientific Abstract:
AIM: Age and injury cause structural and functional changes in coronary artery smooth muscle cells (caSMCs) that influence the pathogenesis of coronary artery disease. Although paracrine signalling is widely believed to drive phenotypic changes in caSMCs, here we show that developmental origin within the fetal epicardium can have a profound effect as well. METHODS AND RESULTS: Fluorescent dye and transgene pulse-labelling techniques in mice revealed that the majority of caSMCs are derived from Wt1(+), Gata5-Cre(+) cells that migrate before E12.5, whereas a minority of cells are derived from a later-emigrating, Wt1(+), Gata5-Cre(-) population. We functionally evaluated the influence of early emigrating cells on coronary artery development and disease by Gata5-Cre excision of Rbpj, which prevents their contribution to coronary artery smooth muscle cells. Ablation of the Gata5-Cre(+) population resulted in coronary arteries consisting solely of Gata5-Cre(-) caSMCs. These coronary arteries appeared normal into early adulthood; however, by 5-8 months of age, they became progressively fibrotic, lost the adventitial outer elastin layer, were dysfunctional and leaky, and animals showed early mortality. CONCLUSION: Taken together, these data reveal heterogeneity in the fetal epicardium that is linked to coronary artery integrity, and that distortion of the coronaries epicardial origin predisposes to adult onset disease.